EDITORIAL COMMENT

In this study, the authors meticulously investigated, in vitro, a causative explanation for previous observations made in vivo, including endothelial cell dysfunction, endothelial marker expression, and apoptosis in diabetic patients[1] and animal models.[2] The authors observed that HG levels downregulated endothelial cell markers but upregulated col-IV expression in human cavernous endothelial cells. In a recent study, the same group described similar findings in vivo in a novel rat model for type 2 DM. These rats displayed blood glucose concentrations >300 mg/dL that persisted for >12 weeks, reaching ≤500 mg/dL at the end of this period.[3] In vivo, a reduced expression of rat endothelial cell antigen 1 in the corpus cavernosum of diabetic rats was observed. Furthermore, the endothelium had a "patchy" appearance, but the control rats had an intact endothelial lining of the cavernous sinuses. Col-IV is present in the endothelial basement membrane, and changes in its expression have been identified in diabetes-associated diseases, such as diabetic nephropathy.[4,5] In our previous study, we found thickening of the subendothelial basement membranes, indicating that the overlying endothelium might indeed be responsible for this observed effect (Fig. 1).[3] Although these changes were striking, no studies were undertaken to further elucidate a pathophysiologic effect. With the present study, the authors reveal a possible direct pathophysiologic role of elevated blood glucose levels as an explanation for those previously observed alterations.[2]

ENDOTHELIAL CELL PROLIFERATION AND SURVIVAL: A NOVEL TREATMENT TARGET?

A severe deterioration of endothelial function in the erectile tissue has been repeatedly described in animal models for both type 1 and type 2 DM. However, clues regarding the pathophysiologic mechanisms of this loss of function are generally lacking. The authors show in an elegant fashion that HG levels suppress endothelial function, as illustrated by tube formation and LDL uptake assays.[2] In addition, the HG concentrations decreased cell proliferation while increasing mitochondrial fragmentation and apoptosis. These observations provide evidence for the direct role of HG concentrations in the loss of endothelial cells in diabetic corpus cavernosum tissue. These are in agreement with previous findings demonstrating that the erectile tissue of diabetic patients with ED has an increased endothelial apoptotic index compared with nondiabetic, non-ED cavernosal samples. Additionally, the apoptotic levels were found to correlate with endothelial dysfunction, as assessed in a preoperative stage by the Penile Nitric Oxide Release Test and duplex scan echocardiography.[1] In recent studies, it has been shown that rho-kinase is upregulated in the erectile tissue of diabetic ED-prone rats.[6,7] Furthermore, this upregulation has been linked to endothelial apoptosis.[8] Chronic treatment of these rats with a rho-kinase inhibitor decreased the endothelial apoptotic index.[8] These insights suggest an important role for rho-kinase regulation in the pathophysiology of diabetic ED.

The results outlined by the present study provide valuable information that will assist us in better understanding the mechanisms behind endothelial dysfunction in the penis of diabetic patients. Additional studies aimed at investigating the interplay between HG concentrations and rho-kinase expression and activity are warranted to gain a better insight into these complex mechanisms. In addition to rho-kinase, the link between HG and the generation of free oxygen radicals in the cavernous endothelium could be another interesting avenue of research to elucidate future treatment targets for diabetic ED.[9]

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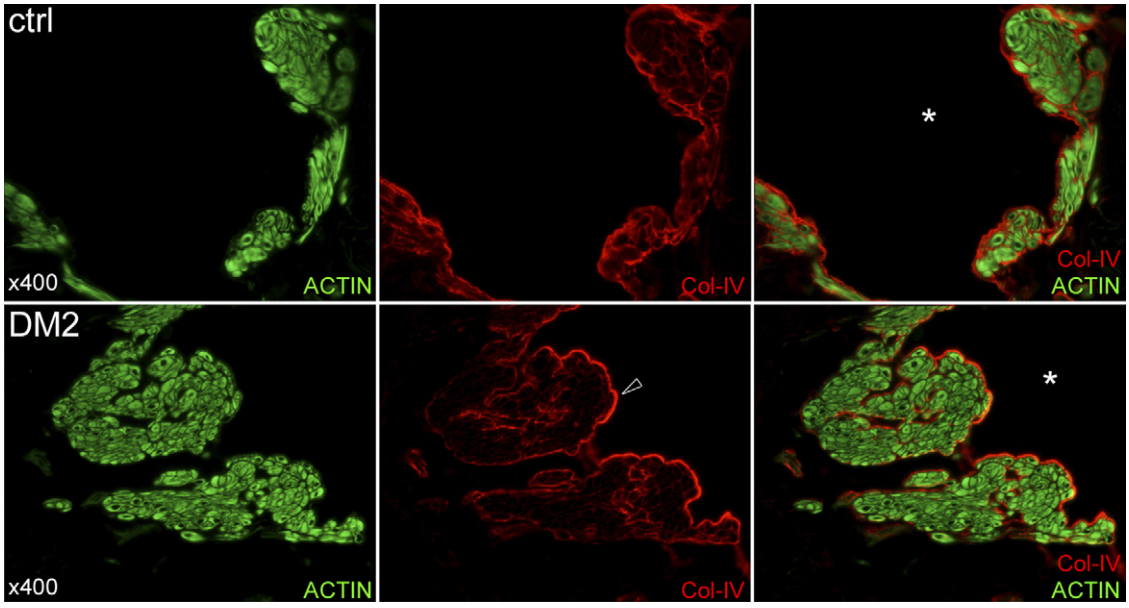

Figure 1. Rat corpus cavernosum in healthy and diabetic rats. Type 2 DM induced as specified in the study by Albersen et al.[3] Midpenile sections immunostained with antibody against col-IV tagged with secondary Alexa 594 (red)-conjugated antibody. Tissues counterstained with Alexa 488-conjugated phalloidin (green) for F-actin, as described previously.[3] Original magnification ×400. *Lumen of sinusoid. Arrowhead indicates thickened subendothelial basement membrane, corroborating observation by Ning et al[2] that endothelial cells secrete greater Col-IV levels when exposed to HG concentrations in culture medium.